

Gene Section

Review

ATMIN (ATM interactor)

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Abstract

Review on ASCIZ/ATMIN, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Keywords

Apoptosis, dynein, DNA damage, transcription factor, lung

Identity

Other names: ASCIZ, ZNF822

HGNC (Hugo): ATMIN

Location: 16q23.2

Local order: Gene orientation: centromere -5' ASCIZ/ATMIN 3'-telomere. ASCIZ/ATMIN is flanked towards the centromere by CENPN (in the same transcriptional orientation) and towards the telomere by C16orf46 in opposite transcriptional orientation (NCBI Gene view, gene ID 23300, version 3-Jun-2014).

Note: The gene was originally reported to encode an ATM-substrate Chk2-interacting Zinc-finger protein and referred to by the name ASCIZ in NCBI/Genbank, before the official gene name was changed to ATMIN by HGNC.

DNA/RNA

Description

The human ASCIZ/ATMIN gene contains five exons over 11497 bases.

The main transcript results from splicing of exon A, parts of exon C, and exons D and E and gives rise to the "full-length" protein containing 823 amino acids with four Zinc-fingers. Two alternative transcripts - comprising either exon B, part of exon C and exons D and E, or a longer exon C and exons D and E - give rise to a shorter 667-residue protein with only two Zinc-fingers.

The mouse ASCIZ gene structure may be simpler with only four exons and single main mRNA encoding an 818-residue protein similar to the human 4-Zinc-finger product.

Transcription

In Northern and Western blot experiments, the two main isoforms of ASCIZ/ATMIN are expressed at relatively similar levels in a wide range of human tissues and all cancer-derived cell lines tested (McNees et al., 2005).

Northern blots of various mouse tissues also indicate relatively similar expression levels in a wide range of organs (Jurado et al., 2010).



Diagram 1. Genomic context of the human ASCIZ/ATMIN gene. Numbers indicate the nucleotide positions on chromosome 16 (location 16q23.2). Arrows indicate the 5' to 3' orientation of each gene. Modified from NCBI Map Viewer.

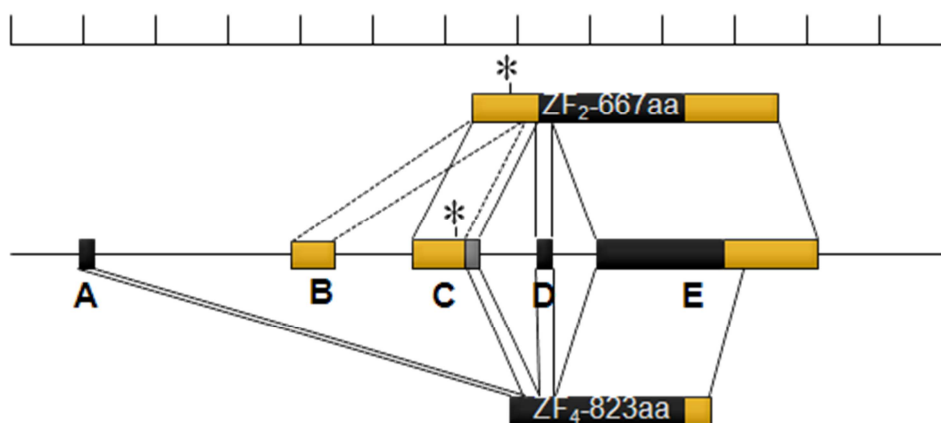


Diagram 2. ASCIZ/ATMIN gene structure and main alternative splice isoforms. ASCIZ/ATMIN contains 5 exons (A-E, center) that are spliced to two main open reading frames based on NCBI AceView. The lower splice isoform accounts for ~85% of transcripts collected in NCBI AceView and encodes an 823 amino acid residue protein with four N-terminal Zinc-fingers. The upper splice isoforms represent ~15% of transcripts and encodes a 667 residue protein with two N-terminal Zinc-fingers. Protein coding sequences are indicated by black boxes; non-coding exon sequences are indicated by open boxes; the grey part of exon C contains coding sequences when spliced into the 4-Zinc-finger transcript, but is out-of-frame as part of the 2-Zinc-finger transcript. The asterisk indicates an in-frame stop-codon in the 5'-UTR of the 2-Zinc-finger isoform. The scale bar on top represents 1 kb per notch.

Pseudogene

Two ASCIZ/ATMIN pseudogenes have been detected on chromosome 9 (LOC643342) and chromosome 12 (LOC100418940).

Protein

Note

The human ASCIZ protein occurs in two isoforms. The more abundant long isoform contains 823 amino acid residues with a mass of 88.3 kDa. The shorter isoform contains 667 residues with a mass of 72.3 kDa.

The two isoforms are identical except that the first 156 residues (including the first two Zinc fingers) of the longer form are missing in the shorter protein.

Mouse ASCIZ contains 818 amino acids and is generally similar to the longer human isoform. Human and mouse ASCIZ exhibit atypical electrophoretic mobility on SDS-PAGE Western blots with an apparent mass of ~115 kDa rather than the predicted ~88 kDa (McNees et al., 2005). The aberrant mobility is unlikely to be caused by post-translational modifications, as similar mobility retardation is also observed with bacterially

expressed recombinant fragments encompassing the SQ/TQ cluster.

Description

ASCIZ contains four (or two in the shorter isoform) C₂H₂ Zinc-fingers at the N-terminus, a so-called core domain, and a C-terminal transcription activation domain.

Human ASCIZ contains 20 potential ATM/ATR kinase phosphorylation sites, most of which are clustered in an SQ/TQ cluster domain coinciding with the transcription activation domain (Heierhorst et al., 2011).

11 of these sites are TQT motifs and represent binding sites for the DYNLL1 protein (Rapali et al., 2011; Jurado et al., 2012a).

Expression

Based on Western blots, the ASCIZ protein is ubiquitously expressed at similar levels in all mouse tissues, with slightly higher levels in brain and testis (Jurado et al., 2010).

Protein expression has not been systematically analysed in human tissues but is expected to be similar to mRNA expression profiles by Northern blots suggesting ubiquitous expression (McNees et al., 2005).



Diagram 3. Topology of the ASCIZ protein. Only the long form is depicted. The shorter form is identical except for lack of the N-terminal 156 residues including the first two Zinc fingers (ZF). Lollipops indicate the 20 SQ/TQ motifs that are potential ATM/ATR kinase phosphorylation sites, including the 11 TQT motif DYNLL1-binding sites in the transcription activation domain.

Localisation

The ASCIZ protein is predominantly, if not exclusively, located to the nucleus but not the nucleolus (McNees et al., 2005; Kanu and Behrens, 2007).

The protein forms discrete sub-nuclear foci after treatment with methylating and oxidating DNA base damaging agents (McNees et al., 2005; Rapali et al., 2011).

Function

ASCIZ was originally identified as an ATM/ATR-substrate and Chk2-interacting protein involved in the DNA base damage response (McNees et al., 2005), and later independently re-isolated as an ATM-interacting protein (Kanu and Behrens, 2007). However, based on recent genetic analyses its main role seems to involve essential developmental functions such as a Zinc-finger transcription factor (Heierhorst et al., 2011).

Knockout mice that completely lack *Asciz/Atmin* die late during gestation (Jurado et al., 2010; Kanu et al., 2010) and exhibit a range of severe organogenesis defects, including most strikingly a complete absence of lungs (Jurado et al., 2010). An N-ethyl-N-nitrosourea (ENU)-generated mouse mutant, *gaspig-6*, that contains a missense mutation of a Zinc-chelating Cys residue in the third Zinc-finger domain of *Asciz/Atmin* also dies during late gestation with overall similar phenotypic defects to the *Asciz/Atmin* null mice, including absent or hypomorphic lungs (Goggolidou et al., 2014). Conditional *Asciz/Atmin* KO mice generated using B lymphoid-specific *Cd19-Cre* (Loizou et al., 2011) or *Mb1-Cre* (Jurado et al., 2012b) have reduced peripheral B cell numbers due to increased apoptotic cell death during B cell development in the bone marrow.

The most highly downregulated gene in *Asciz*-deficient cells is the dynein light chain subunit *Dynll1* (Jurado et al., 2012a). Strikingly, *DYNLL1* protein can in turn bind to about a dozen individual sites - mostly encompassing TQT motifs - in the ASCIZ transcription activation domain (Rapali et al., 2011; Jurado et al., 2012a) and thereby inhibit its transcriptional activity in a concentration-dependent manner (Jurado et al., 2012a), which provides a feedback mechanism to maintain stable *DYNLL1* protein levels. The ability of ASCIZ to regulate expression of and bind to the *DYNLL1*-like dynein light chain (called *Cutup*) is conserved in *Drosophila* (Zaytseva et al., 2014).

The importance of *DYNLL1* as an ASCIZ target is highlighted by findings that B cell developmental defects in conditional *Mb1-Cre Asciz* KO mice can be rescued by ectopic expression of *DYNLL1*, or simultaneous KO of the pro-apoptotic protein *Bim* whose activity is inhibited by *DYNLL1* (Jurado et

al., 2012b). Likewise, in *Drosophila*, RNAi knockdown of ASCIZ or *Cutup* lead to similar developmental defects, which in case of *dASCIZ* RNAi can be rescued by *Cutup* overexpression (Zaytseva et al., 2014).

The role of ASCIZ in DNA damage responses remains unclear. Loss of ASCIZ leads to increased cell death in response to methylating or oxidating DNA damage in human, mouse and chicken cells (McNees et al., 2005; Oka et al., 2008; Jurado et al., 2010; Kanu et al., 2010), and increased basal IgV gene conversion rates in the chicken DT40 B cell line (Oka et al., 2008). ASCIZ focus formation in response to methylating agents depends on *DYNLL1* (Jurado et al., 2012a), but it is not known whether this also involves its transcription factor function. The B cell developmental defect of conditional *Asciz/Atmin* KO mice could not be rescued by deletion of *tp53* or complementation with a pre-arranged B cell receptor transgene (Jurado et al., 2012b), supporting a DNA damage-independent mechanism as cause of the B cell deficiency. ASCIZ was earlier reported to be required for ATM protein stability (and thus termed ATMIN) (Kanu and Behrens, 2007), but this was shown to be incorrect in several subsequent studies (Jurado et al., 2010; Loizou et al., 2011; Zhang et al., 2012). ASCIZ was reported to regulate ATM activation by DNA damage-independent chromatin perturbations (Kanu and Behrens, 2007; Zhang et al., 2012) but this was not confirmed in another study (Jurado et al., 2010).

Homology

ASCIZ protein sequences are highly conserved amongst all vertebrates from fish to mammals (Kanu and Behrens, 2007; Jurado et al., 2012a). The ASCIZ protein is structurally and functionally conserved in *Drosophila*, where it also contains four N-terminal Zinc-fingers and a TQT-rich C-terminal transcription activation domain, condensed into only 388 amino acid residues (Zaytseva et al., 2014).

Mutations

Note

No specific disease-associated mutations of ASCIZ/ATMIN have so far been reported in humans, but an *Asciz/Atmin* mis-sense mutation has recently been identified as the cause of the *gaspig6* (*Gpg6*) ENU mouse mutant (Goggolidou et al., 2014).

Germinal

The *gaspig6* mouse mutation was isolated in an ENU mutagenesis screen (Ermakov et al., 2009). *Asciz/Atmin*^{*gpg6*} mice exhibit exencephaly, edema and absent or small lungs (Ermakov et al., 2009)

and a modest kidney cell polarity defect (Goggolidou et al., 2014). Gpg6 mice contain a point mutation that converts the canonical fourth Zinc-chelating Cys residue in the third Zinc-finger domain to a non-chelating Ser residue (Goggolidou et al., 2014). Dynll1 was the most highly reduced mRNA amongst the analyzed transcripts in affected kidneys (Goggolidou et al., 2014).

Implicated in

B cell lymphoma

Note

Cd19-Cre conditional Asciz/Atmin deletion has been reported to cause B cell lymphoma in ~40% of mice (whose genetic background was not specified) before 1 year of age (Loizou et al., 2011), but deletion via Mb1-Cre (which is more efficient than Cd19-Cre during early B lymphoid stages) in C57BL/6 mice did not lead to B cell lymphoma until at least 2 years of age (Jurado et al., 2012b). Irrespective of genetic background, no lymphomas were observed when Asciz/Atmin was deleted in earlier haematopoietic stem/progenitor cells via Mx1-Cre (Jurado et al., 2012b) or Vav2-Cre (Cremona and Behrens, 2014).

Embryonic development/organogenesis

Note

Germline mutations of Asciz/Atmin in mice lead to late embryonic lethality (Jurado et al., 2010; Kanu et al., 2010; Goggolidou et al., 2014). Mice exhibit exencephaly, complete absence of lungs in the Asciz null mutation or a combination of absent and small lungs in the Asciz/Atmin^{gpg6} point mutant, cardiac defects with oedema, and kidney defects.

Haematopoiesis/B cell development

Note

Conditional Asciz/Atmin deletion during early B cell developmental stages in mice in the bone marrow leads to peripheral B cell deficiency, which is more severe with Mb1-Cre (Jurado et al., 2012b) than Cd19-Cre (Loizou et al., 2011). Pan-haematopoietic inducible Asciz/Atmin deletion in adolescent mice via Mx1-Cre also leads to a statistically significant but modest and well tolerated anemia (Jurado et al., 2012b).

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